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EXAMINER	
ROGERS, JAMES WILLIAM	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,045	CHAU ET AL.	
	Examiner	Art Unit	
	JAMES W. ROGERS	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-56* is/are pending in the application.

4a) Of the above claim(s) *24-28,30-32,34-38 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6 and 9-23,29,33,39,43-49,51-52 and 54-56* is/are rejected.

7)☐ Claim(s) *50 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments to the claims filed 12/28/2007 has been entered. Any rejection not addressed in the action below from the previous office action filed 09/28/2007 has been withdrawn.

Claim Objections

Allowable Subject Matter

Claims 50 and 53 are objected to for depending upon rejected claims however their subject matter would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 1st and 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 9-23,29,33,39,43-49,51-52 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically regarding claims 1 and 12-13, while there is written support for the specific oligopeptide linker IPVGLIG cleavable by MMP-2 there is no written support

for oligopeptide linkers that are cleavable by serine proteases or matrix metalloproteases. Note that the species MMP-2 does not define the genus of metalloproteases recited in claims 1 and 12-13. Regarding claim 2 while there is support for a plurality of drugs for use in the drug conjugate there is no written support that more than one type of linker may be used on the same drug conjugate. It is suggested by the examiner that applicants delete the recitation of "additional linkers" from claim 2.

Claims 1-6 and 9-23,29,33,39,43-49,51-52 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a for the oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2, does not reasonably provide enablement for a linker that is cleaved when the conjugate is exposed to a digestive enzyme selected from the group consisting of serine proteases and matrix metalloproteinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a conjugate for targeting a drug to a tissue comprised of a polymeric carrier, a drug molecule and an oligopeptide linker. The instant specification fails to provide information that would allow the skilled artisan to practice the prevention of the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation.

Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to a conjugate for targeting a drug to a tissue that has overexpressed a digestive enzyme comprised of a polymeric carrier, a drug molecule and an oligopeptide linker linking the drug and polymeric carrier.

(2) The breadth of the claims:

Claim 1 embraces a conjugate comprised of a polymeric carrier a drug molecule and a linker between the drug and carrier, the linker reads on any peptide or protein capable of being cleaved by digestive enzymes selected from serine proteases and matrix metalloproteinases. The specification only enables a linker comprised of the following oligopeptide sequence IPVGLIG cleavable by MMP-2 and fails to provide guidance on other types of linkers or what structural characteristics should be present to give a linker this cleavable functionality. The claims are very broad as the linker is defined by function only.

(3) The state of the prior art:

The state of the art regarding drug conjugates comprising peptide linkers is high. However, the state of the art for using peptide linkers cleavable by any digestive enzyme is very low or does not exist. This is verified by applicants own specification which states "a digestive enzyme that cleaves oligopeptides will typically exhibit strong selectivity for oligopeptides that include one or a small subset of amino acid sequences called recognition sequences". Thus the skilled artisan must experiment to find a peptide that is cleavable by a select digestive enzyme by performing an assay; a select digestive enzyme will not cleave any peptide sequence because the digestive enzyme is very selective. Applicants specification further states "As is further described herein and as is known in the art, the specificity and recognition sequence of a particular digestive enzyme may be determined by comparing the rate at which it cleaves different polymers within a given family (e.g., oligopeptides or oligosaccharides having different sequences". Thus sequences that may be quite similar may have very different selectivity's for a certain digestive enzyme and only a few that are selected by assay have the desired cleavage motif. Thus the predictability of which peptide linkers will have the desired cleavage motif for a given digestive enzyme is low since a virtual library of peptides must be assayed and screened in order to find the peptide(s) with the desired characteristics.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to other peptide linkers besides the oligopeptide sequences IPVGLIG cleavable by MMP-2 is completely lacking. The specification as filed does not speak on or show any working examples or any studies performed on other cleavable peptide sequences. The specification only enables the linker to be selected from the specific oligopeptide sequences IPVGLIG cleavable by MMP-2. In each example, only the previous sequences are provided, guidance on the use of other peptide linkers and the enzymes which cleave those peptide linkers is not provided. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

(7) The quantity of experimentation necessary:

The instant claims read on a conjugate comprised of a polymeric carrier, a drug molecule and a linker between the drug and carrier, the linker reads on any peptide or protein capable of being cleaved by digestive enzymes selected from serine proteases and matrix metalloproteinases. As discussed above the specification fails to provide any support for the use of peptide linkers besides the oligopeptide sequence IPVGLIG which is cleavable by MMP-2. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. It is considered by the examiner to be undue experimentation for the skilled artisan to assay thousands of peptides in order to provide those peptides that exhibit the desired structural motif that is digestible by a specific digestive enzyme. Genetech, 108 F. 3d at 1366 states that " a

patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the specification is enabled for linkers comprised of the oligopeptide sequence IPVGLIG cleavable by MMP-2, but is not enabled for the broad limitation of any linker comprising a peptide or protein capable of being cleaved by digestive enzymes selected from serine proteases and matrix metalloproteinases. It is suggested by the examiner to include the specific peptide sequence above into the dependent claims to remove this rejection

Response to Arguments

Applicant's arguments filed 12/28/2007 have been fully considered but they are not persuasive.

Applicants assert that there is adequate written description within the specification and enablement for the limitations within claims 1-2 and 12-13. Applicants assert that the specification cites several references which disclose methods for determining cleavage motifs for digestive enzymes, such as substrate phase display libraries, position scanning peptide libraries and mixture-based peptide libraries. Applicants assert these references provide reasonable amount of guidance for determining the recognition sequences in the claimed conjugates and these methods would be routine to one of ordinary skill in the art. Thus applicants surmise one skilled in the art would have no difficulty in determining additional sequences that can be cleaved

by the enzymes specified within claim 1 and this would be undue experimentation. Applicants state they have clearly shown how one of ordinary skill in the art can determine the cleavage motif of a target enzyme **when it is not yet known**, determine peptide substrates for known enzymes and identify sequences which are labile to a target enzyme. Applicants also assert that the methodology used to prepare the conjugates of the examples can be used with other peptide linkers since peptides generally contain the same or similar functional groups. Thus applicants surmise the examiner has provided no evidence that the methods of synthesis and/or assays described in the examples cannot be used with other peptide linkers. Applicants assert that the examiner is silent and provides no evidence in regards to how the references and assays described are undue experimentation.

Regarding the written description rejection, the relevance of the above assertions is unclear. It appears as though the entirety of applicant's arguments is based on an **invitation to experiment** using technology in methods for determining cleavage motifs for digestive enzymes. An invitation to experiment is insufficient in regards to written description, the specification must reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not shown that they had possession of any peptide sequences other than IPVGLIG which is cleavable by MMP-2. Applicants seem to be relying on the argument that it would have been obvious to one of ordinary skill in the art to use the methodologies described in the prior art cited within applicants specification to determine cleavage motifs for digestive enzymes. A description that does not render

a claimed invention obvious does not sufficiently describe that invention. But a description that renders obvious a claimed invention does not necessarily satisfy the written description requirement. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405. Also see In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original). It is the position of the examiner that applicants have not described their invention in a detailed enough manner to give support for their broadly disclosed invention within claims 1,12 and 13. Applicants have only described a narrow subset of peptide sequences that are known to be cleaved by digestive enzymes. The number of species described is insufficient to provide support for the very broad genus of any peptide cleavable by a serine protease or matrix metalloproteinase. There is essentially no nexus between what is described and what is claimed and there is no reason to believe that someone skilled in the art would have immediately envisioned applicants claimed invention. Applicants have essentially only given an incomplete plan on how the peptide sequences may be found and synthesized. The plan is incomplete because applicants have only described vague information or general ideas that may or may not be workable in order to find a digestive enzyme that is overexpressed in a

diseased tissue (the enzyme as applicant's state may not even be known) and then developing a sequence that is cleaved by that specific enzyme.

Regarding the enablement rejection as in the above written description remarks by the examiner the relevance of applicant's assertions is unclear. As already stated above applicants appear to be relying on the argument of an **invitation to experiment** using technology in methods for determining cleavage motifs for digestive enzymes and it would be obvious to the skilled artisan to conduct such experiments/assays. This argument is not persuasive in view of the enablement rejection above. Applicants are essentially stating that an assay to find what peptides are cleavable by a very broad genus of digestive enzymes is not undue experimentation. The examiner disagrees because as stated in the rejection above the fact that an assay must be performed to find the right peptide sequence supports the examiners view that predictability in discovering peptides that are cleavable by specific digestive enzymes is low because the enzyme is very selective. Thus an assay must be performed so that the peptides that are cleavable by a specific enzyme can be found. The time to experiment and discover the small subset of sequences that have the desired structural characteristics would be undue for one skilled in the art. Applicants' assertion that the methodology of the examples can be used to make other peptides is also found unpersuasive. The examiner has clearly shown that discovering peptides that are cleavable by the specific digestive enzymes claimed is unpredictable. Therefore the lack of working examples outside of the peptide linker IPVGLIG, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically within claim 4 the recitation that the size of the polymeric carrier is larger than the renal excretion limit is indefinite. The phrase "size of the polymeric carrier is larger than the renal excretion limit" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention as to the size of the polymeric carrier. It is suggested by the examiner to delete the phrase "size of the polymeric carrier is larger than the renal excretion limit". The examiner suggests limiting the type of the polymeric carrier and by a MW range supported in the specification.

Response to Arguments

Applicant's arguments filed 12/28/2007 have been fully considered but they are not persuasive.

Applicants assert that they have defined the phrase within their specification adequately because one of ordinary skill in the art would understand the phrase "renal excretion limit" to mean the size and/or MW which a given polymer is readily cleared from the renal system and the size varies from one polymer to another as evidenced by the references within the specification and cited in applicants response.

The relevance of this assertion is unclear. While it is known in the art as shown by applicants that microparticles which are too large exhibit marked inhibition on renal clearance, it is not clear what size would preclude renal clearance because the physical size of a specific polymer that would preclude clearance is not claimed nor adequately described within the specification. One of ordinary skill in the art when reviewing applicant's claims could not ascertain what polymers are excluded by the functional limitation "renal excretion limit" without a recitation of an actual physical limitation on the size of a specific polymer. It is strongly suggested by the examiner that applicants limit claim 4 by an actual size limitation for the polymeric carrier supported within the specification because a recitation of renal excretion limit is indefinite with respect to the size of the carrier that would be excluded.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6,9-13,17,21,29,33,39,43,47,51-52 and 54-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Copland et al. (WO 01/68145 A2).

Copeland discloses antineoplastic agents such as doxorubicin conjugated to enzyme-cleavable peptides comprising amino acid recognition sequences and the use of such agents in the targeted treatment of cancers including breast and ovarian. The enzyme-cleavable peptides included (MMP) recognition segments such as MMP-2. See

abstract, pag 2 lin 15-pag 3 lin 32, pag 17 lin 8-pag 21 lin 14, pag 33 lin 5-10 and pag 53 lin 3-30. Regarding the limitation in claims 1,12 and 13 on a polymeric carrier, The Copeland patent specifically mentions that enzyme cleavable peptide can be substituted with a capping group such as PEG, that can contain up to 10 monomeric units. See pag 42 lin 19-pag 43 lin 20. Also since the enzyme selective peptide sequences are sequences in a larger polypeptide the rest of the peptide not cleaved by the digestive enzyme can be considered as a polymer carrier, since peptides are poly amino acids. Regarding claim 4 since the claim does not set forth in actual polymer or MW that would satisfy the prophetic limitation "renal excretion limit" the claim fails to further limit the polymer carrier of claim 1, therefore the polymer carriers of Copland (either PEG or the remaining non cleaved peptide sequence) meets applicants limitation. Regarding claim 17 Copeland specifically mentions that the pharmaceutical compositions also include a pharmaceutically acceptable carrier. See pag 47 lin 23-31.

Response to Arguments

Applicant's arguments filed 12/28/2007 have been fully considered but they are not persuasive.

Applicants assert that Copeland does not suggest compositions containing a polymeric carrier. Applicants assert that the PEG moiety described within Copeland is not a polymer but an oligomer. To support their argument applicants cite a reference by Deymour that states an oligomer is a polymer containing from 2-10 repeat units.

The relevance of these assertions is unclear. Firstly by applicants own arguments the definition of the PEG molecule within Copeland is an oligomer, however

oligomers as defined by applicants **are polymers** with 2-10 repeat units, thus it appears applicants have inadvertently supported the position of the office. Regardless of applicant's definition above the examiner defined a polymer as evidenced from the disclosure of Hawley, in The Condensed Chemical Dictionary, 14th ed. as a macromolecule formed by the chemical union of 5 or more identical combining units (monomers). An oligomer is defined by Copeland as a combination of 2-5 monomer units. Since the disclosure of Copeland teaches PEG moieties with up to 10 monomer units it is a polymer.

Applicants further assert that because the claimed conjugate requires at least three distinct components: polymeric carrier, drug and linker the polymer and linker cannot be the same molecule such as a peptide as suggested by the examiner.

The examiner disagrees with this statement. Applicant's claims as currently amended does not exclude peptides, proteins or polyamino acids from being the polymeric carrier. Therefore as stated above, since the enzyme selective peptide sequences are sequences in a larger polypeptide the rest of the peptide not cleaved by the digestive enzyme can be considered as a polymer carrier, since peptides are poly amino acids which are **polymers** themselves.

Applicants assert Copeland does not suggest polymeric carriers having a size larger than the renal excretion limit.

As described above this claim is indefinite as to what sizes would be excluded by this limitation. Therefore since the claim fails to further limit claim 1 the examiner

conducted the search based on polymeric carriers that would meet the limitation of claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6,9-14,17,18,21,22,29,33,39, 43,44,47-48,51-52 and 54-56 are rejected under 35 U.S.C. 102(b) as being unpatentable by Duncan et al. (WO 98/56425, cited in last office action) in view of Copeland et al. (WO 01/68145 A2).

Duncan discloses prodrugs and the method to make them; the prodrugs are activatable by digestive enzymes, in which the drug (including doxorubicin and methotrexate) is connected covalently to a linker (including peptides), which is further connected to a hydrophilic polymer (including dextran). See abstract, page 6 lin 22-33, page 8 lin 34-page 9 lin 22, page 10 lin 10-11, page 11 lin 15-27 and claims 2-4. Regarding claims 9,10 and 13 Duncan used the prodrugs to treat mice with tumors. See page 8 lin 34-page 9 lin 22 and ex. 1-2. Regarding claim 11 Duncan specifically claims a pharmaceutical composition comprising an excipient (claim 17). Regarding claims 54-56 since the active ingredients of the pro-drugs within Duncan are the same as the actives claimed by applicants they will have the same effects when administered to a subject in need. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case or either anticipation or obviousness has been established, Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

Duncan while disclosing prodrugs that are activated by digestible enzymes and peptide linkers is silent on if the linkers are digested by serine proteases and matrix metalloproteinases overexpressed by the tissue.

Copeland discloses antineoplastic agents such as doxorubicin conjugated to enzyme-cleavable peptides comprising amino acid recognition sequences and the use of such agents in the targeted treatment of cancers. The enzyme-cleavable peptides included (MMP) recognition segments such as MMP-2. See abstract, pag 2 lin 15-pag 3 lin 32, pag 17 lin 8-pag 21 lin 14 and pag 53 lin 3-30.

It would have been prime facie obvious at the time of the invention to a person of ordinary skill in the art to modify the peptide linkers disclosed in Duncan and add the peptide sequences disclosed within Copeland. The motivation for combining them would be to produce an advantageous drug conjugate comprising a chemotherapeutic drug such as doxorubicin or methotrexate linked to a polymeric carrier such as dextran through an oligopeotide linker cleavable by MMP-2. One with skill in the art would have had a reasonable expectation of success in substituting/modifying the peptide sequences of Copeland with the linkers Duncan because the linkers are related in that they are used to target tissue and are cleavable by digestive enzymes thus the peptides are related in their use and function. The advantage of modifying the linkers of Duncan with the MMP-2 cleavable peptides within Copland would be that the that the prodrug would be targeted to tissue where MMp-2 is over expressed such as carcinomas tissue, thus the compounds are inactive or significantly less active upon administration to non-diseased tissue, thus lowering the toxicity. Thus, the claimed invention, taken as a whole was *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 12/28/2007 have been fully considered but they are not persuasive.

Applicants assert that Duncan does not disclose a conjugate containing an oligopeptide segment that is cleaved by a digestive enzyme which is overexpressed by a tissue. Applicants further assert that Duncan requires administration of an enzyme conjugate

The relevance of this assertion is unclear. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Clearly the examiner noted in the rejection above that Duncan is silent on linkers that are digested by serine proteases and matrix metalloproteinases that are overexpressed by tissue, whcih is why the reference was combined with Copeland.

Applicants assert that as disclosed above Copeland does not disclose a composition containing a polymeric carrier as claimed. The remarks by the examiner above are incorporated herein, that is Copeland does disclose a composition containing a polymeric carrier.

Applicants assert that one would not be motivated to combine Duncan and Copeland because Copeland teaches away from polymeric carriers. Applicants assert Copland teaches away because as already argued above the PEG moiety of Copeland

is an oligomer. Applicants further state that because Copeland is silent on renal excretion limit it teaches away form the claimed invention.

The remarks by the examiner above is incorporated herein, that is Copeland does disclose a composition containing a polymeric carrier and meets the limitation of claim 4 since it is indefinite and not further limiting.

Applicants further assert that Duncan teaches away from a linker that is cleaved by a digestible moiety because Duncan leaves the impression that one must co administer an enzyme conjugate to achieve overexpression.

The relevance of this assertion is unclear. Firstly the limitation within independent claims 1 and 12 that the tissue overexpresses a digestive enzyme is just an intended use of the conjugate. Since the structure of Duncan is essentially the same as applicants claimed invention it will be able to perform the same intended use. Secondly applicants are once again attempting to show nonobviousness by attacking references individually where the rejections are based on combinations of references. Clearly since Duncan and Copeland are related in that they are used to target tissues that are cleavable by digestive enzymes thus one of ordinary skill could have envisioned combining the two references. Copeland clearly discloses that digestive enzymes including MMP-2 are overexpressed in cancerous tissue, thus it would have been obvious to one of ordinary skill in the art that peptides containing segments cleavable by MMP-2 would be targeted to such diseased tissue.

Applicants lastly report secondary considerations in which example 12 shows *in vivo* evaluation of the anti-tumor efficacy of dextran-oligopeptide-methotrexate

conjugates. The average tumor size decreased by 92% when dextran-oligopeptide-methotrexate and dextran-methotrexate compared to free methotrexate. Applicants surmise that linking methotrexate to a polymeric carrier such as dextran increases the half-life of the drug by decreasing renal elimination. Applicants assert that the above results show unexpected results in view of the teaching of Duncan which requires coadministration of an enzyme in order for the drug conjugate to be effective.

Firstly applicants interpreted the results of example 12 wrongly; tumor size decreased by 92% when dextran-oligopeptide-methotrexate and dextran-methotrexate compared to PBS solution not free methotrexate. Secondly example 12 shows a very specific polymer carrier-oligopeptide-drug that is much narrower than what is actually claimed within independent claims 1, 12 and 13. The specific carrier is dextran, the drug is methotrexate MTX and the linker peptide is IPVGLIG, thus applicants can at best only argue that the specific conjugate above showed unexpected results. It is noted by the examiner that the only claims specific enough to read on the dextran-IPVGLIG-MTX are claims 50 and 53 which as described above have allowable content. Secondly figure 13 shows the results of example 12 and the tumor suppression of dextran-oligopeptide-methotrexate and dextran-methotrexate are nearly identical. Since Duncan clearly discloses dextran conjugated to methotrexate applicants have not shown an example which differentiates their claimed invention from Duncan. In fact the results show little in the way of unexpected results since the tumor size over time of the conjugate closest to the teachings of Duncan (dextran-methotrexate) are essentially the same as applicants invention (dextran-oligopeptide-methotrexate).

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James W. Rogers, Ph.D. whose telephone number is (571) 272-7838. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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